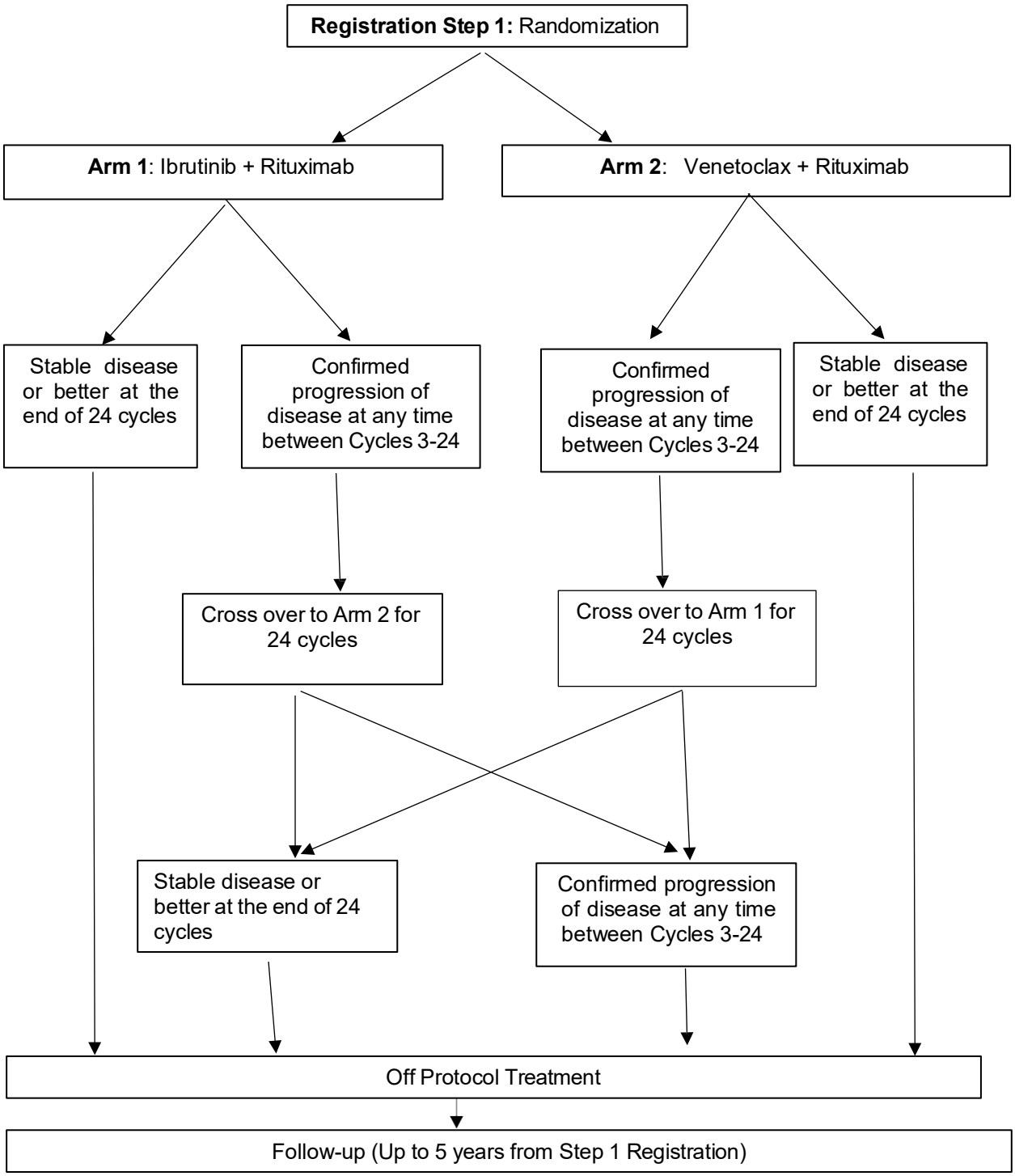
SCHEMA


Registration Step 1: Randomization
Arm 1: Ibrutinib + Rituximab
Arm 2: Venetoclax + Rituximab
Stable disease or better at the end of 24 cycles
Confirmed progression of disease at any time between Cycles 3-24
Confirmed progression of disease at any time between Cycles 3-24
Stable disease or better at the end of 24 cycles
Cross over to Arm 2 for 24 cycles
Cross over to Arm 1 for 24 cycles
Stable disease or better at the end of 24 cycles
Confirmed progression of disease at any time between Cycles 3-24
Off Protocol Treatment
Follow-up (Up to 5 years from Step 1 Registration)

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a participant to be considered eligible for registration in OPEN. Section 5 may be printed and used to by the site, but is not to be uploaded in RAVE (unless specially stated).For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG SDMC in Seattle at 206/652-2267 or myelomaquestion@crab.org prior to registration. NCI policy does not allow for waiver of any eligibility criterion (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm).

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient participant scheduling without exceeding the guidelines. **If Day 14 or 28, falls on a weekend or holiday, the limit may be extended to the next working day.**

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5.1 Registration Step 1: Initial Registration/Randomization

Disease Related Criteria

a. Participants must have had a confirmed diagnosis of Waldenström's macroglobulinemia (WM)/Lymphoplasmacytic Lymphoma (LPL). Participants must have measurable disease as determined by IgM protein quantification (see Section 10.1a).
- **IgM Spike:** ≥500 mg/dL (≥5 g/L)
- **Extramedullary Disease:** The manifestation of a lymphoid mass outside of the bone marrow, resulting in enlargement in extramedullary organs such as the lymph nodes or spleen.

  Note: all participants must have measurable IgM spike, but are not required to have extramedullary disease.

b. Testing to establish baseline disease status must be performed within 28 days prior to registration.

c. Participants must have at least one of the criteria to require therapy for WM including:
- anemia,
- thrombocytopenia,
- neuropathy related to WM,
- symptomatic hyperviscosity or serum viscosity levels greater than 4.0 centipoises,
- WM associated glomerulonephritis or renal disease, bulky disease, or constitutional symptoms.
  - Constitutional symptoms can be described as:
    - unintentional weight loss ≥10% within the previous 6 months prior to Screening;
    - Fevers higher than 100.5°F or 38.0°C for 2 or more weeks prior to Screening without evidence of infection;
    - Night sweats for more than 1 month prior to Screening without evidence of infection;
    - Clinically relevant fatigue which is not relieved by rest due to WM.

Prior/Concurrent Therapy Criteria

d. Participants who require ongoing use or received a moderate or strong CYP3A inducer, moderate or strong CYP3A inhibitor, P-gp inihibitor within 7 days prior to the first dose of study drug will be excluded from the study. If such participants can be safely switched to an alternative agent, then the participants will be eligible to enroll.

e. Participants must not have had prior systemic therapy. Prior therapy with rituximab will be allowed as long as the last rituximab dose was at least 6 months prior to registration.

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Clinical/Laboratory Criteria

f. Participants must be ≥ 18 years of age.

g. Participants must have history and physical exam within 28 days prior to registration.

h. Participants must have Zubrod Performance Status ≤ 2 (see Section 10.7).

i. Participants must have evidence of adequate renal function, as defined by creatinine clearance (CrCl) ≥ 30 mL/min. Values must be obtained within 14 days prior to registration.

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg})}{72 \times \text{serum creatinine}} \dagger$$

Multiply this number by 0.85 if the participant is a female.

† The kilogram weight is the participant weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.8 mg/dL.

j. Participants must have adequate hepatic function defined by the following within 14 days prior to registration:

1. Total bilirubin ≤1.5 x IULN (institutional upper limit of the norm).

AND

2. AST, ALT and alkaline phosphatase ≤ 3 x IULN

k. Participants must have adequate bone marrow function defined by the following without within 14 days prior to registration*:

1. Platelet count ≥ 50,000 cells/mm^3 and

AND

2. Hemoglobin ≥ 7.5 g/dL

AND

3. Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3

* NOTE: Transfusion and/or Growth factor support is allowed up to 7 days prior to registration.

l. Participants with known human immunodeficiency virus (HIV)-infection are eligible providing they are on effective anti-retroviral therapy and have undetectable viral load at their most recent viral load test and within 6 months prior to registration.

m. Participants must be able to take and swallow oral medication (capsules) whole. Participants may not have any known impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of the study drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection.)

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n. Participants must not be intolerant to rituximab.

o. Participants must not have known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding localized skin and nail bed fungal infections) at study enrollment, or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics) 4 weeks prior to registration.

p. Participants must not be seropositive for hepatitis C (except in the setting of sustained virologic response, defined as undetectable viral load at least 12 weeks after completion of antiviral therapy). HCV testing is only required if clinically indicated or if the participant has a history of HCV.

q. Participants must not consume grapefruit, Seville oranges or starfruit within 3 days prior to the first dose of venetoclax.

r. Participants must not be pregnant or nursing because venetoclax has not been studied in pregnant or nursing women and the mechanism of action is expected to cause fetal harm. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" e.g., implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence, or sterilized partner) and a barrier method (e.g., condom, cervical ring, sponge, etc.). This also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate participant chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures throughout the study and for at least 30 days after competition of therapy.

s. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the participant is currently in complete remission, or any other cancer from which the participant has been disease free for two years or watchful waiting is appropriate in the opinion of the treating physician. Also, malignancy that in the opinion of the Investigator, is considered cured with minimal risk of recurrence within 5 years, is permissible consideration of eligibility for this trial.

Specimen Submission Criteria

t. Participants must be offered the opportunity to participate in specimen banking as outlined in Section 15.1.

Regulatory Criteria

u. Participants ***must*** be informed of the investigational nature of this study and must sign and give informed consent in accordance with institutional and federal guidelines.

For participants with impaired decision-making capabilities, legally authorized representatives may sign and give informed consent on behalf of study participants in accordance with applicable federal, local, and CIRB regulations.

v. As a part of the OPEN registration process (see Section 13.5 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the

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current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.2 Registration Step 2: Crossover Criteria

a. Participants must have been registered and received treatment in the IR or VR arm and must show progression of disease as described in Section 10.2 at any time during Cycles 3-24.

b. In case of transformation to intermediate or high-grade lymphoma or development of Bing-Neel syndrome the participants will not undergo registration step 2 crossover and will be taken off the study.

c. Participants must have Zubrod Performance Status ≤ 2 (see Section 10.7).

d. Participants must have evidence of adequate renal function, as defined by creatinine clearance (CrCl) ≥ 30 mL/min. Values must be obtained within 14 days prior to registration.

$$\text{Calculated Creatinine Clearance} = \frac{(140 - \text{age}) \times (\text{weight in kg})\ \dagger}{72 \times \text{serum creatinine}\ *}$$

Multiply this number by 0.85 if the participant is a female.

† The kilogram weight is the participant weight with an upper limit of 140% of the IBW.
* Actual lab serum creatinine value with a minimum of 0.8 mg/dL.

e. Participants must have no evidence of marked hepatic dysfunction on any recent liver function tests within 14 days prior to registration.

f. Participants must have adequate bone marrow function defined by the following without within 14 days prior to registration*:

1. Platelet count ≥ 50,000 cells/mm^3 and

AND

2. Hemoglobin ≥ 7.5 g/dL

AND

3. Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3

* NOTE: Transfusion and/or Growth factor support is allowed up to 7 days prior to registration.

6.0 STRATIFICATION FACTORS

Participants will be stratified at the time of randomization based on the following criteria:
Prior treatment with rituximab: Yes vs. No.

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